which states "[t]he dispersing principle is cavitation." Cavitation requires water as the dispersion medium. Thus, "anhydrous" or "water reduced" dispersion mediums distinguish the present process from that of Muller 410, which requires water as the dispersion medium.

Applicants again respectfully submit that the wording in the abstract should be carefully and correctly read. The abstract describes only the solubility properties of the carrier disclosed in Muller 410. According to the wording the carrier (or active ingredient, respectively) is "insoluble ..... in water, aqueous media and/or organic solvents" and "when introduced" into these media (i.e. the processed or finalized carrier is subsequently introduced into same) the carrier has special properties (e.g. increased saturation solubility).

Applicants respectfully submit that the abstract of Muller 410 does not describe the dispersion medium in which the carrier is prepared. There is simply no teaching in the abstract of Muller 410 regarding the dispersion medium. The dispersion medium used in Muller 410 to prepare the carrier thereof is **water**, as clearly described throughout the specification thereof. Applicants respectfully submit that the Examiner is improperly reading the abstract of Muller 410 out of context with the entire written description.

In contrast, in the present invention, an anhydrous or water-reduced medium is used as the dispersion medium. The present invention solves the problems associated with using water in a piston-gap homogenizer. It has been found that water vapor creates bubbles in a piston-gap homogenizer, which subsequently implodes (i.e. cavitation) to lead to particle diminution. This problem is avoided by the present invention. Since Muller 410 does not disclose using an anhydrous or water-reduced medium in the piston-gap homogenizer as the dispersion medium, Muller 410 cannot anticipate the claim invention. Furthermore, by teaching to use water as the dispersion medium to produce cavitation, Muller 410 teaches in a direction opposite to the claimed invention.

Applicants now respond to each argument raised by the Examiner. On page 5 of Office Action, second half, the Examiner argues that Applicants had written that the process of the present invention differentiates from Muller 410 by using an

"anhydrous" or "water-reduced" dispersion medium. This argument was rejected by the Examiner because in the 410 patent it is also described that piston-gap homogenization is used for the production of parenteral emulsions, that means dispersing oils. Therefore the use of oils as described in the present application would have been described. Applicants respectfully submit that the Examiner did not differentiate between:

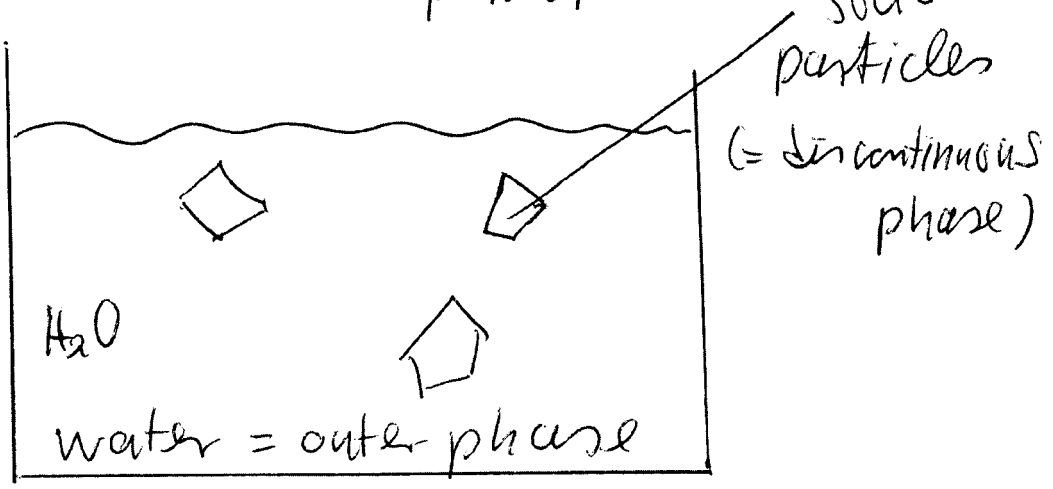
a) outer phase of the dispersion (= continuous phase)

b) dispersed phase (discontinuous phase, = particles to be diminuted).

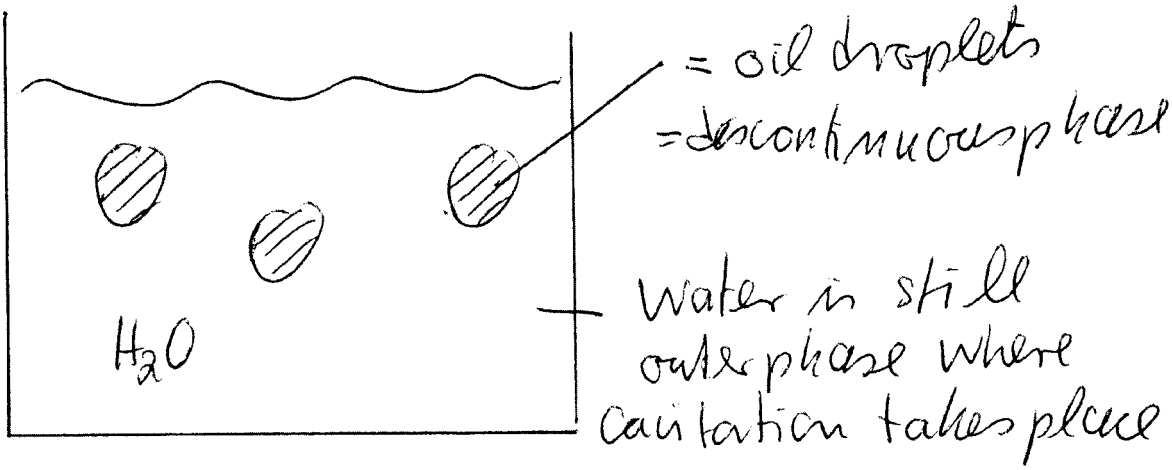
Cavitation is explicitly described in the literature as the one main force for particle diminution. The cavitation resulting in particle diminution takes place in the outer phase. In Muller 410 the outer phase is **water**, solid particles are diminuted. In the parenteral fat emulsions the outer phase is still water. The oil is not the continuous phase, therefore no size reduction process was described in the Muller 410 having non-aqueous outer phase and showing simultaneously similar size reduction efficiency as homogenizing water dispersions.

In the present invention, the outer phase is non-aqueous (or water-reduced). See the comparison between the claimed invention and the structure disclosed in Muller 410.

Muller, 410



parenteral fatemulsions, o/w emulsions



present invention

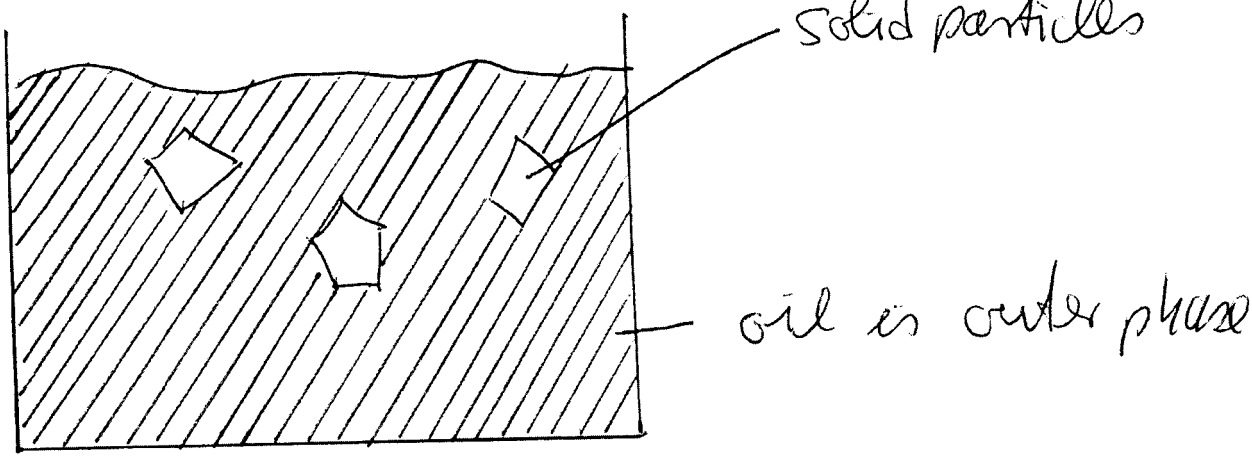


Figure 1

On page 6 of pending Office Action, second half page, and 1st paragraph on page 7 the Examiner correctly states that in Muller 410 a compound is added which is insoluble, only sparingly soluble or moderately soluble in water, and/or organic solvents, and

a) that the compounds in Muller 410 and in the present invention have the same (or similar) properties and
b) are similar in structure or being even identical molecules.

This is logic, because a compound which is insoluble in water and in organic media can be homogenized in water leading to a nanosuspension (particles in water!) but the same compound can now also be homogenized in an organic medium, in which it is insoluble (e.g. oil) leading in this case also to a nanosuspension, but an **oily** nanosuspension.

However, even if the same molecules are used, this does not anticipate all processes using the same molecules to lead to an identical product. Furthermore, the aqueous nanosuspension (Muller 410) is not the same as the presently claimed oily nanosuspension. For example, when micronized particles are produced starting from the same molecule, the same particle size, leading to the same size of the final micronized product, but using different processes, one process does not anticipate the other process. In the case a rotor-stator colloid mill is used, this does not anticipate the process of jet milling. As a further example, regarding nanosuspensions, the process of ball milling by the company élan (previously Nanosystems) (US 5,145,684, 1992, G. Liversidge, et al.) uses the same starting material (molecule and size), leads to nanocrystals of identical or similar size, nanocrystals also dispersed in water, but does not anticipate the process of using homogenization in water as described in Muller 410. There are exactly the same nanocrystals of fenofibrate on the market, the product Tricor (élan process, distributor Abbott) and the product Triglide (nanocrystals produced by homogenization). Similarly, the present new process using different dispersion media is not anticipated by Muller 410.

Using the Muller 410 process, it is necessary to remove the water from the

water-nanosuspension, dry the nanocrystals (a process in which they just like to aggregate, and aggregates loose their biopharmaceutical advantages such as increase in oral bioavailability), and subsequently redisperse the nanocrystals in an oil for soft capsule filling. A clear advantage of the present invention is that the nanocrystals are directly produced in the oil and can be filled straight away as oily nanosuspension into capsules. Another advantage of the present invention is the faster removal of dispersion medium when producing pellets or tablets. The mixtures with a reduced water content evaporate faster.

On page page 7 of the present Office Action, last paragraph, the Examiner is correct in that the present invention does not exclude water, because apart from water-free media (e.g. oils), also water mixtures are described. The Examiner also correctly describes the different combination features which do not necessarily imply a reduction of the water content of the dispersion medium!

Again, the different modifications of the homogenization process discovered during the invention process:

1. reduction of water:

The general knowledge in the art is that cavitation is the essential force for size reduction in the homogenization process, that means in theory pure water as outer phase should be most efficient, especially when one additionally raises the temperature in the homogenization process to 70-90° C, because at higher temperature, the vapor pressure of water is even higher leading to much more pronounced cavitation, which should lead theoretically to smaller particle size compared to homogenization at room temperature.

In contrast, the first surprising finding was, when reducing the water content, by using water mixtures (or even removing completely the water by using low vapor oils), the efficiency in size reduction remained practically unchanged.

2. exclusion of plastisizer

Against the teaching in the literature, that a plastisizer makes material softer and thus easier to disintegrate by homogenization was not found to be the case.

From this theoretically also a process is covered using 100% water as dispersion medium, but using no plastisizer. Therefore toxicologically critical plastisizers can be avoided. Of course, this plastisizer-free homogenization can also be done with pure water in the outer phase.

3. Reduction of temperature:

In contrast to the state of the art, it was found that the temperature has no effect on the size of the processed substances, which means as advantage of the invention heat-sensitve molecules can be efficiently homogenized at low temperatures. For some molecules this process is even more efficient in size reduction. However, if desired this process can use pure water as outer phase.

On page 9 of the pending Office Action, the Examiner is correct when stating that the present invention does not exclude water. The Examiner has the opinion that in case of using water reduced media cavitation is still present, therefore, there is no difference with Muller 410 for the water-reduced media containing still some water. The Examiner is correct, that depending on the mixture there might still be some cavitation. However, before this invention the teaching of the state of the art was, that having pure water leads to maximum cavitation and thus consequently to highest efficient diminution. Surprisingly, it was found that varying the water content did not affect the size reduction, that means the teaching was wrong, because cavitation is not the major force for size reduction. This discovery allows use of water reduced mixtures having advantages for various pharmaceutical operations (e.g. production of final oral dosage forms). That means in the water-reduced process, even if there should be some cavitation remaining, the new finding is that this is not important for the size reduction process, allowing to use water-mixtures at same or similar efficiency against the previous teaching.

Again, column 20, lines 35-40 of Muller 410 is claim 38. Claim 38 of Muller 410 describes a method in which as part of the process "subjecting at least one solid therapeutically active compound dispersed in a **solvent** to high pressure homogenization....". When one introduces a compound into a **solvent**, - as the word solvent says – the compound would **dissolve**, and not be in the form of small

particles any more. Thus the process of claim 38 of Muller 410 as it is worded will not yield in nanosized particulate carrier particles, because the active ingredient would **dissolve**. The method of claim 38 of Muller 410 yields a **solution**.

In contrast to this, according to the present invention the active ingredient is **dispersed** in a **non-solvent**, i.e. medium, which results in a **suspension**. This suspension is then subjected to high pressure homogenization to yield a nanosuspension. Thus, the Muller 410 patent does not contain any teaching how to produce nanosized solid carriers in a non-solvent medium. For this reason alone, the Muller 410 patent cannot anticipate the claimed invention.

Furthermore, claim 38 of the Muller 410 patent must be read in light of its specification. The Muller 410 patent clearly requires using water as the dispersion medium to cause cavitation, as discussed above. Thus, claim 38 must be interpreted in light of the specification of Muller 410 to require using water as a dispersion medium to provide cavitation.

In contrast, the present invention utilizes an anhydrous or water-reduced dispersion medium to avoid cavitation. For this reason alone, Muller 410 cannot anticipate the claimed invention.

In view of the differences between Muller 410 and the claimed invention, withdrawal of the Section 102 rejection is respectfully requested.

The rejection of claims 1-20 and 22-47 under 35 U.S.C. § 103 as being unpatentable over WO 98/14174 (Desai) in view of U.S. Patent No. 5,104,674 (Chen) is respectfully traversed. The claimed invention is not obvious over Desai in view of Chen for the following reasons.

Chen recites in claim 1:

> A method for producing a microfragmented anisotropic xanthan/protein complex dispersion comprising the steps of forming an aqueous suspension of molecularly intimately complexed xanthan/protein fibers comprising at least 7 weight percent of xanthan gum based on the total solids weight of said fibers, conducting said **aqueous** fiber suspension through a zone of high shear to fragment the fibers under sufficient conditions of shear and duration to reduce substantially all of said fibrs to xanthan/protein complex

microfragments having a maximum dimension of less than about 15 microns."

This means that Chen is using water as dispersion medium and obtains particles in the micrometer range. The aqueous phase contains e.g. polysaccharides, no mixtures of water with other water miscible liquids are described. Thus, the combination of Desai and Chen uses water. For this reason alone, the Section 103 rejection should be withdrawn.

The Examiner states that one of ordinary skill in the art would be motivated to make paclitaxel or itraconazole compositions according to methods disclosed in the cited prior art wherein the methods have been shown to provide advantages of reduced volumes and low toxicity products.

It might be assumable that one would have tried to make such small drug nanoparticles, but the essential question is: Does the disclosure of Desai in view of Chen lead one of ordinary skill in the art to the present invention?

The Examiner admits that in Desai, "the drug is **dissolved** in an organic solvent." See page 3 of the Office Action. In contrast, in the claimed method the matrix material is not dissolved in the anhydrous or water-reduced medium. It remains in solid particle form as a **dispersion**.

Desai teaches the preparation of a **nanoemulsion**, plus subsequent additional steps to obtain drug particles in the nano-meter range. Disruption of large **droplets of a liquid** requires "relatively" low forces (compared to disrupting solids) and appears feasible.

In contrast to this, solids are much more rigid due to their crystalline and solid character. From the Desai disclosure one would **not be motivated** to process **solid drugs** using the same process. For this reason alone, the Section 103 rejection should be withdrawn.

As discussed previously, Applicants have now found that during homgenization using a piston-gap homogenizer, water vapor can be created in the form of bubbles, which subsequently implode. The resulting implosion shock waves lead to particle diminution. However, many materials are destroyed, melted or

otherwise undesirably altered by these violent shock waves. See page 3, last paragraph to page 4, first paragraph, in the present translated application.

Applicants have solved these problem by providing a far more gentler method of obtaining the same particle size without using the implosion shock waves:

1) reducing the temperature of the medium being homogenized; and/or

2) reducing or eleminating the use of water.

As discussed above, prior to the present invention, it was believed throughout the art that cavitation is the main source of diminution, as a consequence high pressure homogenization is generally described in water and especially increased effectiveness is claimed when homogenizing at higher temperatures. The reason for the increased efficiency at higher temperatures is the increased vapour pressure of water at higher temperature which provides increased cavitation. Therefore, the general teaching is the need to use water at higher temperatures to provide increased cavitation formation from water vapor to thereby provide particle diminution.

Contrary to this teaching, according to the present invention homogenization is performed in media other than water (anhydrous) or water reduced, and/or at lower temperatures to reduce or avoid cavitation from water vapor. Surprisingly, a comparable size diminution can be obtained without using destructive implosion shock waves. Contrary, to the general knowledge in the art, Applicants have found that cavitation is not the dominating diminution principle in the present invention. This is further supported by performing homogenization at lower temperatures, e.g. at 0° Celcius or below. A surprisingly similar efficiency in diminution is observed, which is contrary to the general beliefs in the art.

Desai does not disclose homogenizing solid particles and Desai does not address the problems associated with implosion shock waves from water evaporation. For these reasons, the Section 103 rejection should be withdrawn.

Desai homogenizes an emulsion (dispersed liquid in an outer liquid phase), the invention a suspension (i.e. solid dispersed in a liquid outer phase).

Desai dissolves the drug (pharmacologically active agent) in an organic phase which is subsequently dispersed in an outer phase which is subsequently passed

through a high pressure homogenizer. See page 14, lines 12-24 of Desai. This process itself is a well known homogenisation process for an o/w emulsion yielding particles with a mean diameter of 200 nm to 400 nm (e.g. products Intralipid, emulsion for intravenous infusion, marketed since appr. 1960, nowadays company Baxter Healthcare, US). The knowledge that a liquid phase can be dispersed to a size below 1000 nm is known for more than have a century.

Especially from Desai, this conclusion cannot be drawn because Desai uses a special trick to obtain the small particles. One of ordinary skill in the art knows that the formed emulsion droplets lead to very small particles because they "shrink" due to the evaporation of the solvent in the droplets. To get even smaller particles, Desai adds water soluble solvents such as ethanol to the organic phase (page 10, lines 25-27) which easily partitions into the water phase leading to further shrinking of the particles. That means the teaching by Desai is:

a) the drug needs to be dissolved in a liquid dispersed phase;

b) drug nanoparticles can only be achieved using volatile solvents leading to shrinking of the generated nanoemulsion droplets and subsequent formation of a solid particle;

c) especially very small particles need additionally a water soluble solvent.

From this, i.e., from a disclosed emulsion patent with high pressure homogenization, it cannot be concluded that also hard crystalline particles can be processed to nanoparticles (<1000 nm) using this method. As already pointed out, the required dispersion forces for a liquid are dimensions lower than for a crystalline material.

On page 3, last line and page 4, 1st line, of the Office Action, the Examiner states that Deasi decribes the effect of solvents how to make small particles. However, in case of Deasi the solvent is:

a) the dissolution medium for the drug,

b) the inner phase of the emulsion system,

b) it needs to be evaporated to finally yield the small particles (Fig. 1).

In the present invention, the solvent

a) does not dissolve the drug, i.e. the prerequisite of the invention is that the solvent does not dissolve the drug,

b) is the outer phase of the dispersion to be homogenized, not the inner phase,

c) does not need to be evaporated to obtain the particle.

That means the only common thing between Desai and the present invention is that a solvent is used, but in a completely different manner. The teaching by Desai directs one into a completely different direction, that means to the processing of solutions.

The Examiner states on page 4, 1st paragraph of the pending Office Action, that Desai disclosed advantages of small particles and everybody would be motivated to make them.

Firstly, it is correct, that everybody wants to make them, which is secondly known long before Desai and textbook knowledge for decades in Pharmaceutical Technology and Biopharmaceutics. However, the desire to have something does not teach how to make it. The teaching for the present invention is not disclosed in Desai. An expressed desire is not prior art to making the desired something.

Claim 1 of Desai describes a completely different process, and different processing steps of dissolving the active in the solvent etc. It is not identical with claim 1 of the present invention as alleged by the Examiner.

Chen does not solve the many deficiencies of Desai. Chen teaches using high speed stirrers, e.g. as said on page 12. The high shear zone should best have a shear rate of at least about 37,000 inverse seconds, with a turbulent energy dissipation rate sufficient to raise the temperature of the suspension at least about 5° C. through viscous dissipation of input energy to heat.

Page 16 of Chen describes a Gaulin machine, but it states that only particles in the low micrometer range can be obtained and there is no teaching about nanofragments:

> Effective results have been achieved by using a CD150 or a MC15 cell disruptor using a knife edge homogenization element within a closely surrounding impact ring (A.P.Z. Gaulin Corp., Boston, Mass.) at an inlet pressure of at least about 3000 psig and preferably at least

> 10,000 psig to obtain microfragments smaller than fifteen microns preferably smaller than 5 microns in maximum dimension.

In example 1 Chen uses a jet stream homogenizer, which means high pressure honmogenization is disclosed (at least jet-stream): "Microfluidizer model 110Y sold by Biotechnology Development Corporation of...."

Also claim 26 of Chen reads:

> 26. A microfragmented syneresed ionic polysaccharide/protein complex dispersion in accordance with claim 24 comprising microfragments having a mean maximum dimension in the range of from about 2 to about 10 microns.

In contrast, present claim 46 recites particles "5.6 µm or less," which are not included in Chen's particle range of 2 to 10 microns. For this reason alone, the Section 103 rejection should be withdrawn.

In response to the Examiner's arguments on page 10 of the pending Office Action, Applicant respectfully submits that Desai is clearly homogenizing an o/w emulsion, as described e.g. on page 9, lines 22 and 23. Desai prepares an o/w emulsion, the drug is dissolved in the o phase and after homogenizing the coarse emulsion to a fine emulsion, the o phase is evaporated, leading to the precipitation of solid particles after the homogenization process.

In contrast, in the present invention solid particles are homogenized, not an emulsion.

The solvent, the Examiner cites, which Desai is using for washing the particles is different to the one used for dissolving the drug. Desai teaches to use a "suitable" solvent, which means Desai selected for washing the particles a solvent which did not dissolve the particles (in contrast to the solvent used for preparation of the o/w emulsion, which had to dissolve!). Therefore the conclusion of the Examiner, that the first solvent Desai used for preparing the emulsion was not dissolving the drug, is not justified.

In response to the Examiner's arguments on page 10 of the pending Office Action, Applicant submits that Taxol is not insoluble in organic solvents, as the Examiner states. On page 17, lines 14 to 19 Desai states that the drug is dissolved

in a suitable solvent. That means Desai is homogenizing an o/w emulsion with drug dissolved in the droplets of the o phase.

Formation of an emulsion after homogenization is also stated on page 18, lines 12 to 14, also stating again that the drug is dissolved (no particles).

In example 1 Desai dissolves the Paclitaxel (Taxol) in methylene chloride to obtain a solution.

The use of stabilizers to stabilize a suspension is state of the art, therefore Desai does not anticipate something which is not generally known. The present invention does not claim to have invented a stabilizer to stabilize a particle suspension.

At the bottom of page 11 in the pending Office Action, the text cited by the Examiner has been taken out of the context. It is refers to page 16, lines 14 to 26. High shear is used to disperse a "dissolved agent", that means Desai is referring to the homogenization of the o/w emulsion containing dissolved paclitaxel. Furthermore Desai says high shear is used to disperse "suspended" active. Of course, it is easy to disperse an agent with high shear.
However:

1. the term disperse does not include that during the dispersion process a size reduction takes place. From this there is no teaching about size reduction by Desai.

2. Reading the next lines 17-27 it is clear what Desai is describing: The droplets of the nanoemulsion containing the dissolved drug are coated by an albumin layer, transforming the droplets to solid material. Solidification is caused by the heating in the process (albumin denaturates) and by the formed superoxide ions. That means Desai describes an albumin capsule formation and not a size reduction of crystalline material as in the present invention.

In response to the Examiner's arguments on page 12 of the Office Action, as outlined above, Desai is homogenizing an emulsion with dissolved drug, the emulsion does not contain any solid particles. The solid particles are formed after homogenization, when the o phase is evaporated and due to this the drug precipitates.

At the bottom of page 12 in the pending Office Action, the examiner is correct, that solvent evaporation and solvent diffusion are well known processes, but they are not claimed in the present invention. Despite Desai is using solvents also used in these processes, there is no description in Desai that drug was precipitated prior to homogenization. In contrast, Desai refers to dissolved drug in the nanoemulsions.

The Examiner argues Applicant is using the same ethanol as Desai. This is the case, but only if the drug does not dissolve in the ethanol! That means the conditions are very different.

The Examiner is correct, that in example 15 Chen is using a piston-gap homogenizer. However Chen describes the process for microfragmentation, that means the results are microparticles, not nanoparticles. This is confirmed in claim 1 of Chen reciting fibres up to a size of 15 µm. There are no indications, that nanosized material can be achieved.

It is known that piston-gap homogenizers can produce high shear energy, but no person of ordinary skill would assume the process to be suitable for making nanosized material from solid, crystalline drugs, based on Chen. Apart from size up to 15 µm, Chen is using a xanthan/protein complex and no hard solid crystalline material.

In view of the many differences between the claimed invention and the theoretical combination of Desai and Chen, withdrawal of the Section 103 rejection is respectfully requested.

In view of all of the rejections of record having been addressed, Applicants submit that the claimed invention is in condition for allowance and Notice to that effect is respectfully requested.

Respectfully submitted,

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